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Downstream resource utilization following hybrid cardiac imaging with an integrated cadmium-zinc-telluride/64-slice CT device

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Abstract: **PURPOSE:** Low yield of invasive coronary angiography and unnecessary coronary interventions have been identified as key cost drivers in cardiology for evaluation of coronary artery disease (CAD). This has fuelled the search for noninvasive techniques providing comprehensive functional and anatomical information on coronary lesions. We have evaluated the impact of implementation of a novel hybrid cadmium-zinc-telluride (CZT)/64-slice CT camera into the daily clinical routine on downstream resource utilization. **METHODS:** Sixty-two patients with known or suspected CAD were referred for same-day single-session hybrid evaluation with CZT myocardial perfusion imaging (MPI) and coronary CT angiography (CCTA). Hybrid MPI/CCTA images from the integrated CZT/CT camera served for decision-making towards conservative versus invasive management. Based on the hybrid images patients were classified into those with and those without matched findings. Matched findings were defined as the combination of MPI defect with a stenosis by CCTA in the coronary artery subtending the respective territory. All patients with normal MPI and CCTA as well as those with isolated MPI or CCTA finding or combined but unmatched findings were categorized as "no match". **RESULTS:** All 23 patients with a matched finding underwent invasive coronary angiography and 21 (91%) were revascularized. Of the 39 patients with no match, 5 (13%, $p < 0.001$ vs matched) underwent catheterization and 3 (8%, $p < 0.001$ vs matched) were revascularized. **CONCLUSION:** Cardiac hybrid imaging in CAD evaluation has a profound impact on patient management and may contribute to optimal downstream resource utilization.

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Downstream resource utilization following hybrid cardiac imaging with an integrated cadmium-zinc-telluride/64-slice CT device

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Abstract

Purpose Low yield of invasive coronary angiography and unnecessary coronary interventions have been identified as key cost drivers in cardiology for evaluation of coronary artery disease (CAD). This has fuelled the search for non-invasive techniques providing comprehensive functional and anatomical information on coronary lesions. We have evaluated the impact of implementation of a novel hybrid cadmium-zinc-telluride (CZT)/64-slice CT camera into the daily clinical routine on downstream resource utilization.

Methods Sixty-two patients with known or suspected CAD were referred for same-day single-session hybrid evaluation with CZT myocardial perfusion imaging (MPI) and coronary CT angiography (CCTA). Hybrid MPI/CCTA images from the integrated CZT/CT camera served for decision-making towards conservative versus invasive management.

Based on the hybrid images patients were classified into those with and those without matched findings. Matched findings were defined as the combination of MPI defect with a stenosis by CCTA in the coronary artery subtending the respective territory. All patients with normal MPI and CCTA as well as those with isolated MPI or CCTA finding or combined but unmatched findings were categorized as “no match”.

Results All 23 patients with a matched finding underwent invasive coronary angiography and 21 (91%) were revascularized. Of the 39 patients with no match, 5 (13%, $p<0.001$ vs matched) underwent catheterization and 3 (8%, $p<0.001$ vs matched) were revascularized.

Conclusion Cardiac hybrid imaging in CAD evaluation has a profound impact on patient management and may contribute to optimal downstream resource utilization.

Keywords Downstream resource utilization · CZT · SPECT · Cardiac hybrid imaging

Michael Fiechter and Jelena R. Ghadri contributed equally to this work.

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Introduction

In clinical practice diagnosis of coronary artery disease (CAD) has been based on the presence of luminal narrowing of greater than 50% documented by invasive coronary angiography catheterization (CATH). However, it has been recognized over the last decade that many factors other than lumen size and its narrowing, which cannot be comprehensively elucidated by coronary angiography alone, may determine whether or not an anatomical coronary lesion induces ischaemia. Therefore, decision-making towards

revascularization without proof of ischaemia has been recently challenged. In fact, modern guidelines for coronary revascularization [1] stipulate that comprehensive evaluation including proof of ischaemia is mandatory for prognostically relevant target vessel revascularization in chronic stable CAD.

Nuclear myocardial perfusion imaging (MPI) is a well-established method for the evaluation of myocardial ischaemia and coronary computed tomography angiography (CCTA) has been established over the past years as a clinical tool for the assessment of coronary anatomy. The combination of MPI with CCTA has been found to be a valuable gatekeeper for invasive coronary angiography [2] and may help to increase the low yield of elective invasive diagnostic coronary angiography (currently less than 40%) [3]. Cardiac hybrid imaging has emerged as one of the latest methodological advancements, integrating information on anatomy (CCTA) with that from MPI into hybrid images [4]. This allows to directly relate individual myocardial perfusion territories to the subtending coronary arteries. Most studies on hybrid MPI/CT imaging are based on fusion of data from a separate gamma camera and a stand-alone CT scanner, as the unfavourable discrepancy of scan length (short CT and long MPI acquisition time) was hampering the widespread use of hybrid single photon emission computed tomography (SPECT)/CT devices in daily clinical routine. With the introduction of new gamma cameras using a cadmium-zinc-telluride (CZT) detector technique [5–8], scan time has been reduced substantially down to a few minutes [9, 10]. This has paved the way for hybrid SPECT/CT scanners integrating a CZT gamma camera with a high-end 64-slice CT device and has increased the interest in cardiac fusion imaging, further supported by recent results confirming the diagnostic strength [4, 11] and the prognostic value [12] of cardiac hybrid imaging. However, data on the added clinical value of hybrid cardiac CZT/CT imaging in the decision-making for the appropriate treatment strategy are lacking. The aim of the present study was to evaluate in the daily clinical routine the impact of hybrid cardiac MPI and CCTA imaging obtained with an integrated ultrafast CZT/CT device on downstream resource utilization such as invasive coronary angiography and revascularization.

Materials and methods

Patients and study protocol

We included 62 patients without a history of prior coronary artery bypass graft (CABG) who were consecutively referred for the assessment of known or suspected CAD for a same-day single-session hybrid scan with CZT MPI and CCTA to obtain hybrid cardiac images. All patients were

scanned on a CZT/64-slice CT hybrid camera (Discovery NM/CT 570c, GE Healthcare), and the integrated CZT/CT images were reported to the referring physicians who made a decision towards invasive CATH versus conservative management based on the hybrid imaging finding on the one hand and including the clinical history and the symptoms on the other hand. Similarly, in the catheterization laboratory the interventional cardiologist based his/her decision towards revascularization on the hybrid images and the clinical history, integrating the angiographic findings including fractional flow reserve (FFR) at the operators' discretion into the clinical decision-making. Downstream resource utilization within 60 days triggered by the hybrid imaging was assessed, including decision for conservative treatment, invasive angiography and revascularization procedure (CABG or percutaneous coronary intervention, PCI). From each study participant, written informed consent was obtained for the use of their imaging and clinical data for research purposes as approved by the Institutional Review Board.

Image acquisition

All patients underwent a 1-day pharmacological stress/rest SPECT MPI protocol according to the guidelines of the European Association of Nuclear Medicine [13] with adenosine (0.14 mg/kg per min over 6 min) while in patients with contraindications to adenosine ($n=16$) we used dobutamine (incrementally administered, starting at 5 $\mu\text{g/kg}$ per min and increasing at 1-min intervals to a maximal dose of 60 $\mu\text{g/kg}$ per min until 85% of the age-predicted heart rate had been achieved) according to daily clinical routine in our lab. Approximately 60 min after injection of $^{99\text{m}}\text{Tc}$ -tetrofosmin (332 ± 36 MBq), stress MPI images were acquired (5 min) using the CZT/CT camera. This was followed by acquisition of rest MPI with the identical acquisition protocol several minutes [14] after administration of a three times higher dose of $^{99\text{m}}\text{Tc}$ -tetrofosmin (955 ± 169 MBq). MPI scans were acquired using a multi-pinhole collimator (effective diameter aperture of 5.1 mm) and 19 stationary detectors simultaneously imaging 19 different views of the heart as previously reported. In brief, each detector contains 32×32 pixelated (2.46×2.46 mm) CZT elements; the system design allows acquisition without detector or collimator motion, and a 10% symmetrical energy window at 140 keV was used [9]. A low-dose CT scan was performed for attenuation correction of SPECT MPI, which also allows calculation of calcium scoring [15]. Thereafter, all patients underwent contrast-enhanced CCTA with prospective ECG triggering as previously reported [16–18]. Intravenous metoprolol (2.5–25 mg) was administered prior to the examination if necessary in order to obtain optimal image quality for CCTA (target heart rate <65 bpm). All patients

received 2.5 mg isosorbide dinitrate sublingually 2 min prior to the CCTA scan. MPI and CCTA images were fused on a dedicated workstation (Advantage Workstation 4.3, GE Healthcare) projecting the MPI images on the left ventricular epicardial surface obtained from the CCTA using the CardIQ Fusion software package (GE Healthcare) as previously validated [19, 20]. The 3-D volume rendered fusion images enable a panoramic view of the coronary artery tree projected onto the left ventricular myocardial perfusion territories. Cardiac hybrid images can be displayed in standard anterior, posterior, lateral and apical views and in freely selectable angles for standardized documentation and reporting. Effective radiation dose for CCTA was calculated from the dose-length product (DLP) using a conversion coefficient for the chest, $k=0.014$ mSv/(mGy \times cm); for SPECT MPI a conversion factor of 0.0079 mSv/MBq was used.

Cardiac hybrid image interpretation

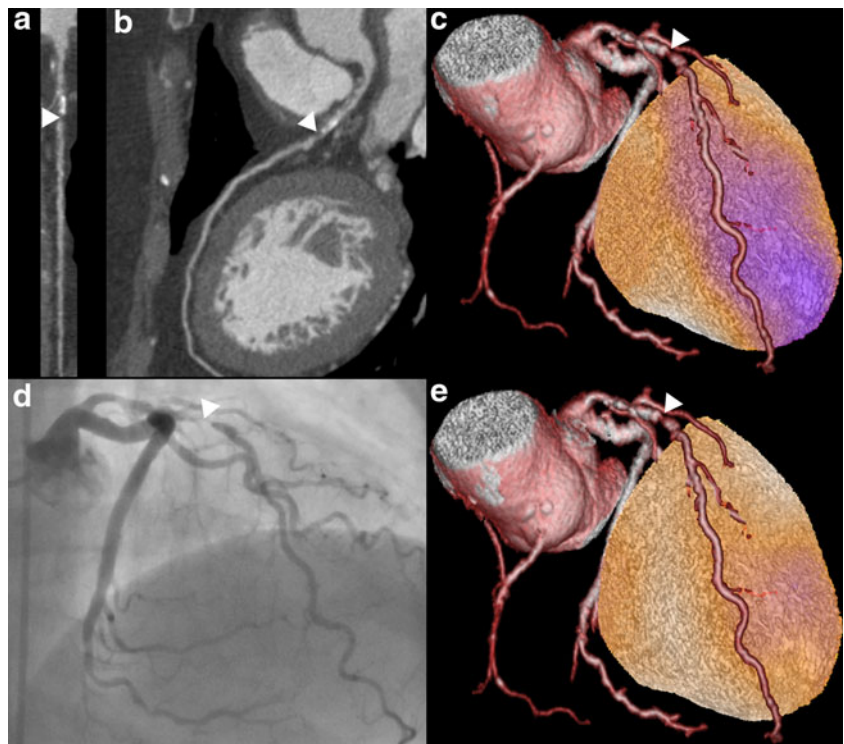
Fused MPI and CCTA images were analysed by two experienced nuclear cardiologists by consensus with regard to functionally relevant coronary stenoses. For each patient, myocardial tomograms were grouped into 20 segments. The following 5-point scoring system was used to grade the segmental radionuclide uptake: 0=normal, 1=equivocal, 2=moderate, 3=severe reduction of radioisotope uptake and 4=absence of detectable tracer in a segment. A pathological scan was defined as one with stress score ≥ 2 in two or more

segments. If a stress defect was associated with a stress defect score of 4 with a rest score of 2 or a rest score ≤ 1 , a scan was classified as reversible perfusion defect. As patient management should be ischaemia driven according to best clinical practice, only reversible defects were considered for the following assignment into “matched” vs “no match” finding. A matched SPECT/CT hybrid cardiac imaging finding was defined as a reversible SPECT MPI defect in a territory served by a coronary artery with a stenosis (defined as narrowing of the coronary luminal diameter $\geq 50\%$, Fig. 1). All patients with normal SPECT and CCTA as well as those with isolated CCTA or MPI finding or combined but anatomically unmatched finding were categorized as no match.

Invasive coronary angiography data acquisition and analysis

Invasive CATH was performed according to clinical standards by experienced interventional cardiologists. Segmentation of the coronary artery tree was performed as described for CCTA. A coronary stenosis was defined as a luminal narrowing $\geq 50\%$. This was based on visual assessment reflecting the clinical routine in our and most other catheterization laboratories worldwide [21, 22]. The FFR was determined as the ratio of the simultaneously assessed pressure in the aorta and in the coronary artery distal to a stenosis during maximal hyperaemia (induced by intravenous adenosine administration via a central vein at 140 $\mu\text{g/kg}$ per min) [22].

Fig. 1 Cardiac hybrid image and angiographic finding. Coronary artery stenosis (*white arrowhead*) in proximal left anterior descending artery is shown in CCTA (**a** multiplanar and **b** curved multiplanar reconstruction), cardiac hybrid imaging with normal perfusion at rest (**e**) and perfusion defect (pink area) at stress (**c**), matching the territory of the coronary artery with stenosis (*white arrowhead*), and invasive coronary angiography (**d**) confirming the coronary stenosis (*white arrowhead*)



Statistical analysis

Quantitative variables were expressed as mean±standard deviation and categorical variables as frequencies or percentages. SPSS 19.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. The chi-square test was applied to compare the revascularization rates between the two different patient groups. A *p* value from the chi-square test of less than 0.05 was considered statistically significant.

Results

All patients (*n*=62) successfully underwent stress/rest CZT MPI and CCTA using the CZT/CT camera. The patient characteristics are given in Table 1.

Overall, the CATH rate was 43% in the study population yielding 96% CAD. CZT revealed 32 patients (52%) with an abnormal MPI with reversibility in 26 patients, while CCTA documented a coronary stenosis in 42 patients (68%) excluding CAD in 20 patients (32%). Three cases with false positive SPECT were corrected into negative by normal CCTA findings. Conversely, a coronary stenosis ≥50% on CCTA but without stress-induced regional perfusion defect was found in 17 patients, while 19 patients had a normal finding on both CCTA and MPI. Cardiac hybrid imaging revealed a matched perfusion defect in 23 patients (38%), whereas 39 patients (63%) had no matched findings. The measurement of FFR was performed in 9 patients (in 12 coronary lesions).

During follow-up, all patients with matched cardiac hybrid findings (*n*=23) were referred to CATH of whom 21 (91%, Fig. 2) subsequently underwent PCI or CABG. Of the two patients without revascularization, one had normal coronary arteries by CATH and the second patient had a small MPI defect and invasive assessment revealed a stenosis with normal FFR (≥0.8) over two lesions, i.e. in the left anterior descending artery (0.82) and in the left circumflex artery (0.89), both of which therefore did not qualify for coronary revascularization [23]. Only 5 of the 39 patients (13%) with no matched hybrid finding (Fig. 2) were sent to CATH and 3 (8%) were revascularized. The reasons for referring a patient to CATH without matched hybrid finding were either severe CAD (left main or three-vessel disease) ≥80% (*n*=2) or massively elevated Agatston coronary calcium scoring (> 1,000; *n*=3). The latter has recently been shown to unmask obstructive CAD in patients with normal SPECT MPI [24]. Revascularization was subsequently performed in three patients despite lack of matched finding as one patient revealed abnormal FFR over a lesion in the left anterior descending artery (0.69) and the other patients showed either severe coronary three-vessel disease or severe stenosis of the left main artery. There was a significantly lower

Table 1 Baseline patient characteristics (*n*=62)

Characteristic	Value
Male, <i>n</i> (%)	47 (76)
Age (years)	
Mean±SD	62±10
Range	40–86
BMI (kg/m ²)	
Mean±SD	28±5
Range	19–46
Cardiovascular risk factors, <i>n</i> (%)	
Obesity (BMI >30 kg/m ²)	18 (29)
Diabetes mellitus	10 (16)
Smoking	18 (29)
Hypertension	42 (68)
Dyslipidaemia	35 (56)
Positive family history	22 (35)
Clinical symptoms, <i>n</i> (%)	
Typical angina pectoris	20 (32)
Atypical chest pain	3 (5)
Dyspnoea	8 (13)
No cardiac symptoms	31 (50)
Clinical findings, <i>n</i> (%)	
Abnormal rest ECG	27 (44)
Abnormal stress ECG	29 (47)
Abnormal echocardiography	4 (6)
Previous cardiac events, <i>n</i> (%)	
Myocardial infarction	5 (8)
PCI	22 (35)
Stent implantation	21 (34)
Current cardiac medication, <i>n</i> (%)	
Aspirin	46 (74)
Beta-blocker	27 (44)
ACE/angiotensin II inhibitor	28 (45)
Statin	41 (66)

BMI body mass index

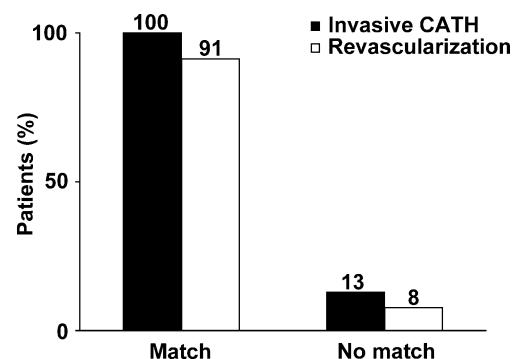


Fig. 2 Downstream resource utilization after cardiac hybrid imaging. CATH coronary angiography catheterization

downstream CATH resource utilization in patients with no matched findings versus those patients with matched cardiac hybrid findings ($p<0.001$). Due to subclinical CAD ($<50\%$ luminal narrowing) preventive medical intervention was initiated in one patient, while in one patient such medication was withdrawn after excluding any lesion by CCTA.

The effective radiation dose for stress/rest SPECT MPI was 10.2 ± 1.5 mSv, for attenuation correction 0.9 ± 0.1 mSv and for prospective triggered CCTA 1.8 ± 0.6 mSv.

Discussion

Our results demonstrate that cardiac hybrid imaging with a CZT/CT device allows efficient comprehensive evaluation of CAD. This has a profound impact on patient management and may contribute to optimal downstream resource utilization. In the present study we have shown that in 91% of patients with a matched finding on cardiac hybrid imaging coronary revascularization was performed, whereas only 8% of patients without matched cardiac hybrid finding were revascularized.

With regard to resource utilization the use of hybrid imaging had a strong impact as 100% of patients with a match but only 13% of patients without match were referred for CATH. As a result, in the patient group with a match the CAD per CATH yield was 96% comparing favourably to the yield of less than 38% recently reported for a similar elective large population [3]. The high CAD yield in our study paved the way for the above-mentioned high rate of revascularization per CATH (91%), which is far superior to figures reported in registries of most European countries, such as for example Germany (36%) [25].

An appropriate selection of patients who will benefit from invasive CATH and eventually from revascularization is crucial not only because of the costs of CATH but also because of its non-negligible rate of procedural in-hospital morbidity and mortality [26, 27]. Although it has been suggested for a long time [28] and repeatedly documented [22] that for best clinical practice functional assessment of coronary lesions is mandatory, invasive CATH has remained not only the gold standard for CAD detection but also for decision-making for or against the need for revascularization. Our results show that hybrid cardiac imaging is an excellent gatekeeper for further evaluation with CATH. In fact, the high yield of CAD and revascularization rate per CATH documents an appropriateness of invasive resource utilization far beyond that reported from large registries of routine clinical practice [3, 25]. By contrast, resource utilization was very low in patients with no hybrid match, in whom a decision towards invasive CATH ($n=5$) was mainly driven by extensive coronary calcification ($> 1,000$ Agatston units), which has recently been shown to unmask CAD in

patients without SPECT MPI abnormalities. Therefore, in the present study a calcium score $>1,000$ triggered a CATH overruling the lack of a matched finding. In three of these five patients justification to revascularize was supported either by FFR or the presence of severe multi-vessel disease including main stem involvement [2]. The clinical value of comprehensive CAD assessment by hybrid CZT/CT imaging lies in the improvement of evidence-based patient selection for coronary revascularization [12, 29]. Although coronary interventions have been shown to successfully reduce ischaemic symptoms and, therefore, improve patients' quality of life, periprocedural adverse events remain important considerations, particularly in low-risk populations. In stable CAD populations revascularizations have failed to confer a prognostic superiority compared to optimal medical therapy [30–33]. However, in patients with moderate to large ischaemia revascularization may be the most effective strategy to reduce the amount of jeopardized myocardium and, consequently, improve prognosis [34]. As hybrid findings have been shown to be superior in predicting adverse events over isolated findings [12], it appears appropriate that these findings are the predominant target of revascularization. In this context our results show that the implementation of a hybrid CZT/CT camera in daily clinical routine confers an added value for evidence-based decision-making and optimization of adequate downstream resource utilization. Patients with intermediate to high pre-test probability are among those who most likely may benefit from noninvasive evaluation by hybrid imaging. However, in view of the fact that most patients referred for elective invasive coronary angiography reveal normal coronary arteries, even lower pre-test probability patients may be candidates for a hybrid approach as long as unnecessary invasive angiographies can be avoided. A larger study would be needed to provide final proof of cost-effectiveness of the hybrid method, which was beyond the scope of the present pilot study.

We acknowledge the following limitations: A potential limitation of the present study is the fact that all patients underwent two noninvasive tests cumulating radiation exposure to the patients. However, several algorithms may be implemented into hybrid imaging such as for example stress-only MPI [35] to reduce radiation. In addition, CZT cameras offer the potential of a low-dose/low-dose 1-day protocol as the count-rate linearity allows subtraction of the counts of the first scan avoiding the need for a threefold increase of the second scan [36]. Finally, although patients were included consecutively, there was no randomization to different treatment options due to the observational nature of this pilot study on the downstream resource utilization. However, our results support the notion that use of a CZT/CT hybrid device in the daily clinical routine may favourably affect resource utilization. Nevertheless, this may also

depend on the awareness of the clinicians about the availability and performance of hybrid imaging as well as on the clinical environment accepting noninvasive imaging as guidance for revascularization.

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Conflicts of interest None.

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